CHEMISTRY LETTERS, pp. 991-994, 1992.

Practical Preparation of Chiral 4-Substituted 2-Oxazolidinones

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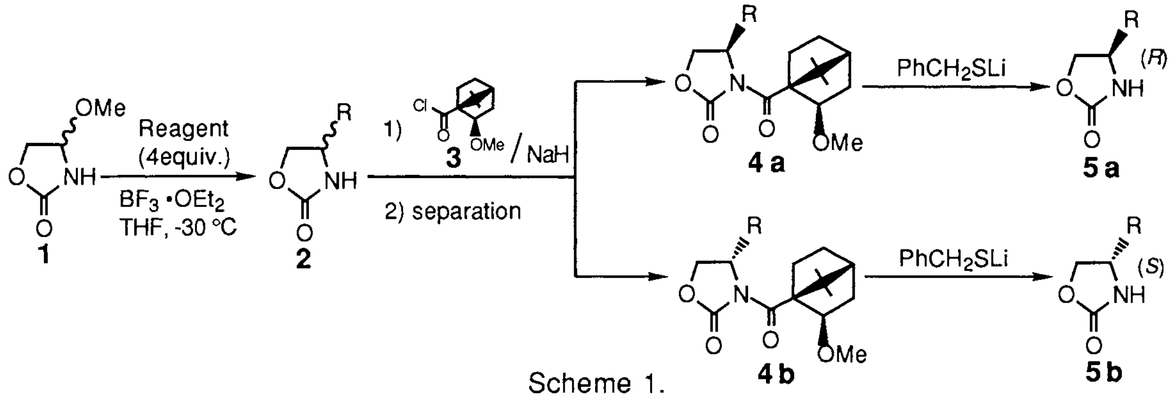
A versatile and practical route to both enantiomers of a wide variety of 4-substituted 2-oxazolidinones from the parent heterocycle is provided by regioselective substitutions via 4-methoxy derivative followed by chromatographic separation of the diastereomers derived from N-2-*exo*-methoxy-1-apocamphanecarbonylation.

The chiral 4-alkyl- and 4-aryl-2-oxazolidinones have been widely utilized as excellent auxiliaries in the Evans' asymmetric strategy which is highly successful in the chiral construction of a number of natural products.[1)] Apart from the (*S*)-4-substituted-2-oxazolidinones readily obtainable from naturally occurring L-α-amino acids,[2)] the antipodal (*R*)-isomers and the well-designed auxiliaries, which are often needed for high levels of the required diastereoselection, are not so easily accessible in a preparative quantity.



Scheme 1.

This paper describes the versatile and efficient method for the preparation of both enantiomers of 4-substituted 2-oxazolidinones, which could serve as the Evans' auxiliaries as well as the chiral synthetic precursors for unusual α-amino acids,3) starting from the parent heterocycle, 2-oxazolidinone, by way of the regioselective substitutions at the 4-position followed by facile optical resolution (Scheme 1).

The 4-methoxy-2-oxazolidinone (**1**) , readily available from anodic oxidation of 2-oxazolidinone in methanol,4) was treated with the organocuprate-$\mathrm{BF_3}$ reagents at -30 °C to result in smooth replacement of the 4-methoxy group by a wide variety of *primary* to *tertiary* alkyls and aryls.5) In certain cases, higher order cuprates were preferable (Entries 5,6, and 9).

Table 1. Preparation of Diastereomeric 4-Substituted 2-Oxazolidinones (**4a** and **4b**)

Entry	Reagent	R	Yield / %a)			αb)
			2	→ **4a**	+ **4b**	
1	$\mathrm{Me_2CuCN(MgBr)_2}$	Me	66	32	46	1.78
2	BuCuCNLi	Bu	66	34	48	2.38
3	*iso*-PrCuCNMgBr	*iso*-Pr	67	43	46	1.71
4	*tert*-BuCuCNMgCl	*tert*-Bu	66	46	43	1.50
5	$\mathrm{(PhCH_2)_2CuCN(MgCl)_2}$	$\mathrm{PhCH_2}$	60	48	50	1.56
6	$\mathrm{Ph_2CuCNLi_2}$	Ph	72	42	47	1.69
7	$\mathrm{CH_2{=}CHMgBr}$	$\mathrm{CH_2{=}CH}$-	52	37 c)	36c)	1.41
8	$\mathrm{PhC{\equiv}CLi}$	$\mathrm{PhC{\equiv}C}$-	69	33 c)	36 c)	1.61
9	(α-Naphthyl)$_2$CuCNLi$_2$	α-Naphthyl	70	37 c)	40 c)	1.28
10	*cyclo*-$\mathrm{C_6H_{11}CH_2CuCNMgBr}$	*cyclo*-$\mathrm{C_6H_{11}CH_2}$-	69	44 c)	40 c)	1.58

a) Isolated yields. b) The separation factor, α, is the ratio of R_f values for diastereomers **4a** and **4b** on 0.2 mm silica gel plates (Merck, Kieselgel 60 F_{254}) with dichloromethane as a developing solvent. c) Absolute configurations are tentative.

As shown in Table 1, alkenyl and alkynyl functions were also introduced in good yields with organo magnesium or lithium reagents in place of the cuprates (Entries 7 and 8).

Treatment of 4-substituted 2-oxazolidinones (**2**) thus obtained with (1*S*)-2-*exo*-methoxy-1-apocamphanecarbonyl chloride6) (**3**) gave the readily separable mixture of N-acylated diastereomers **4a** and **4b**, which could be thoroughly separated by usual gravity-driven column chromatography on silica gel. The large separation factors, α, as indicated in Table

1, implied the extremely easy operations for complete separation to the optically pure isomers. The sterically congested and conformationally fixed 2-*exo*-alkoxy-1-apocamphane carboxylic acids seem to be the versatile auxiliaries of choice for facile optical resolution of a variety of 4-(or 4,5-) substituted 2-oxazolidinone heterocycles.[7)]

Typical procedure (Table 1, Entry 3) is as follows. To the THF (10 cm^3) solution of cuprous cyanide (396 mg, 4.4 mmol) and anhydrous lithium chloride (374 mg, 8.8 mmol; dried at 150 °C for 1 h), *iso*-propylmagnesium bromide (5.2 cm^3, 0.78 M in THF) was dropwise added at -30 °C under argon atmosphere. After stirring for 30 min., 4-methoxy-2-oxazolidinone (119 mg, 1.0 mmol) and $BF_3{\bullet}OEt_2$ (0.25 cm^3, 2.0 mmol) were added successively and it was kept at -30 °C overnight. The reaction was quenched by addition of satd. NH_4Cl solution (0.5 cm^3) and the product was purified by column chromatography on silica gel (CH_2Cl_2 / AcOEt = 7 : 3 as eluent) to yield 4-*iso*-propyl-2-oxazolidinone (**2**) (86.8 mg, 67%) as colorless crystal. Sodium hydride (248 mg, 6.2 mmol) was added to the solution of 4-*iso*-propyl-2-oxazolidinone (**2**) (395 mg, 3.1 mmol in 20 cm^3 of THF) and the resulted suspension was stirred at room temperature for 1 h. The solution of (1*S*)-2-*exo*-methoxy-1-apocamphanecarbonyl chloride (**3**) (derived from the acid (791 mg, 4.0 mmol) and $SOCl_2$ (40 cm^3)) in THF (10 cm^3) was added, and the mixture was stirred at room temperature overnight. After filtration through silica gel pad, the filtrate was concentrated *in vacuo*, and the residue was purified by column chromatography on silica gel (CH_2Cl_2 / Hexane = 1 : 1 to CH_2Cl_2 as eluent) to yield **4a** (404 mg, 43%, Rf=0.60) and **4b** (432 mg, 46%, Rf=0.35) both as colorless crystals. Deacylation of 2-oxazolidinones **4a** and **4b** with lithium benzylmercaptide[8)] under cooling proceeded smoothly to give the enantiomerically pure 4-substituted 2-oxazolidinones **5a** and **5b**, respectively (Table 2), except for the case of highly hindered 4-*t*-butyl derivatives. The $LiBH_4$-MeOH system was required for the deacylations[9)] of the *t*-butyl derivatives

Among the chiral heterocycles thus obtained, the (*R*)-enantiomers and 4-α-naphthyl derivatives would be of particular interest as chiral auxiliaries for asymmetric synthesis. The ring-opening of the chiral 2-oxazolidinones would give the 2-amino alcohols which are readily oxidized to a variety of enantiomeric α-amino acids.[3)]

Table 2 . Deacylations of **4a** and **4b** to 4-Substituted 2-Oxazolidinones (**5a** and **5b**)[a)]

Entry	R	Yield / %		$[\alpha]_D$ ($CHCl_3$)	
		5a	**5b**	**5a**	**5b**
1	$PhCH_2$-	90	96	+62.5°	-62.5°
2	*iso*-Pro	54	69	-5.1°	+5.3°
3	*tert*-Bu[b)]	43	27	+22.8°[c)]	-22.2°[c)]
4	Ph	75	90	-57.1°	+56.1°
5	α-Naphthyl	72	99	-227.5°	+228.1°
6	PhC≡C-	99	99	+26.7°	-27.9°
7	*cyclo*-$C_6H_{11}CH_2$-	67	93	+15.9°	-14.9°

a) With $PhCH_2SLi$ (1.5 equiv.) at 0 °C for 2 hr. b) With $LiBH_4$ (8 equiv.) and MeOH (16 equiv.) in THF at r.t. c) In methanol.

In conclusion, a practical route to both enantiomers of a wide variety of 4-substituted 2-oxazolidinones from the parent heterocycle is now available.

References

1) D. A. Evans, J. Bartroli, and T. L. Shih, *J.Am.Chem.Soc.*, **103**, 2127 (1981); D. A. Evans, *Aldrichimica Acta,* **15**, 23 (1982) and references cited therein.
2) P. G. M. Wuts and L.E. Pruitt, *Synthesis*, **1989**, 622.
3) N. A. Sasaki, C. Hashimoto, and P. Potier, *Tetrahedron Lett.*, **28**, 6069 (1987); P. J. Maurer, H. Takahata, and H. Rapoport, *J.Am.Chem.Soc.*, **106**, 1095 (1984); P. L. Beulieu, *Tetrahedron Lett.*, **32**, 1031 (1991).
4) P-C. Wang, *Heterocycles*, **9**, 2237 (1985).
5) S. Ishibuchi, Y. Ikematsu, T. Ishizuka, and T. Kunieda, *Tetrahedron Lett.*, **32**, 3523 (1991).
6) T. Ishizuka, S. Ishibuchi,and T. Kunieda, *Tetrahedron Lett.*, **30**, 3449 (1989); T. Ishizuka, K. Kimura, S. Ishibuchi, and T. Kunieda, *Chem.Pharm.Bull.*, **38**, 1717 (1990).
7) H. Matsunaga, K. Kimura, T. Ishizuka, M. Haratake, and T. Kunieda, *Tetrahedron Lett.*, **32**, 7715 (1991).
8) R. E. Damon and G. M. Coppola, *Tetrahedron Lett.*, **31**, 2849 (1990).
9) In addition, 4-*tert*-butyl-2-oxazolidinones (**4a** and **4b**) underwent partial endocyclic cleavage to yield (2*R*)-and (2*S*)-2-(2-*exo*-methoxy-1-apocamphanecarbonylamino)-3,3-dimethylbutan-1-ols in 27% and 50%, respectively.

(Received April 6, 1992)